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(54) Title: ENTERIC COATED PRAVASTATIN BEAD FORMULATION

(57) Abstract

An enteric coated pravastatin bead formulation is provided which includes pravastatin, optionally a basifying agent such as MgO or $CaCO_3$, and an enteric coating formed of a methacrylic acid copolymer which may be a methylacrylate/methacrylic acid copolymer or a methylmethacrylate/methacrylic acid copolymer, and plasticizer such as diethyl phthalate and a dusting of talc. The enteric coated formulation has good resistance to deterioration at pH less than 3, but has good drug release properties at greater than 4 and provides for increased bioavailability and increased LDL and TG lowering compared to pravastatin formulations which do not include an enteric coating and do not provide release throughout the small intestine for prolonged absorption time.

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ENTERIC COATED PRAVASTATIN BEAD FORMULATION

Reference to Other Applications

This is a continuation-in-part of Application Serial No. 09/083,597 filed May 22, 1998.

Field of the Invention

The present invention relates to an enteric coated pravastatin formulation, which is in the form of beads, which includes pravastatin, which is sensitive to a low pH environment of less than 3; optionally a basifying agent; and an enteric coating, and optionally an antiadherent coating, such formulation being resistant to acid degradation of pravastatin in the stomach but releases pravastatin at pH's greater than 4 as found in the small intestine.

Background of the Invention

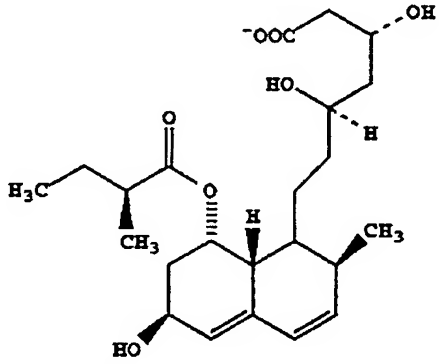
Enteric coatings have long been used to inhibit release of drug from tablets and beads and/or prevent the leakage of acid to the inside of the bead or tablet containing acid labile drug. The enteric coatings are resistant to stomach acid and depending on the composition and/or thickness thereof, they begin to dissolve and allow for the release of drug in the intestines. Some examples of coatings previously employed are beeswax and glyceryl monostearate; beeswax, shellac and cellulose; and cetyl alcohol, mastic and shellac as well as shellac and stearic acid (U.S. Patent No. 2,809,918); polyvinylacetate and ethyl cellulose (U.S. Patent No. 3,835,221); neutral copolymer of polymethacrylic acid esters (Eudragit L30D) (F.W. Goodhart et al, Pharm. Tech., pp 64-71, Apr., 1984); copolymers of methacrylic acid and methacrylic acid methyl ester (Eudragits), or a neutral copolymer of polymethacrylic acid esters containing metallic stearates (U.S. Patent Nos. 4,728,512 and 4,794,001 to Mehta et al.).

Hydroxypropylmethyl cellulose phthalate (HPMCP) is available from Shin-Etsu Chemical Co., Ltd. which recommends application of this polymer, for use in enteric coatings, in its natural acidic form from organic solvents. This material starts its dissolution process at pH 5.0.

Stafford, J.W., Drug Dev. Ind. Pharm., 8(4), 513-530 (1982) and Bloor, J.R. et al, Drug Dev. Ind. Pharm., 15(14-16), 2227-2243 (1989) describe the use of HPMCP as its totally neutralized form (treated with sodium hydroxide) as an enteric coating applied from aqueous systems. Aqueous systems are preferred due to environmental concerns and flammability/explosion concerns with solvents.

Pharmaceutical compositions which include a medicament which is unstable in an acidic environment such as the stomach will require an enteric protective coating to prevent release of such medicament prior to reaching the intestines.

Pravastatin, an HMG CoA reductase inhibitor disclosed in U.S. Patent No. 4,346,227 to Terahara et al and having the formula



is sensitive to a low pH environment and is very unstable at pH 3 or less as found in the stomach. The primary degradation product of pravastatin is the inactive isomer 3-α-hydroxy-isopravastatin as disclosed by J. Triscari et al, "Gastrointestinal Absorption of Pravastatin in Healthy Subjects", J. Clin. Pharmacol., 1995; 35:142-144. The acid instability of pravastatin reduces its bioavailability and results in degradation of pravastatin and formation of

significant levels of the inactive isomer 3-α-hydroxy-isopravastatin in the serum following oral administration of pravastatin. It has also been found that pravastatin is absorbed rapidly from immediate release dosage forms with the major absorption site being the upper intestines, that is the duodenum.

U.S. Patent No. 4,661,162 to Kurihara et al discloses an enteric soluble pharmaceutical dosage form which includes an active ingredient surrounded by a membrane which is formed of a mixture of an enteric-soluble polymer and a polyanionic polymer which is soluble in or permeable to a liquid having a pH greater than or equal to 2.

As indicated by Kurihara et al, the active ingredient may be "the sodium salt of M-4 carboxylic acid, an anti-hyperlipidemic agent described in U.S. Patent No. 4,346,227." The polyanionic polymer may be alginic acid, polypectinic acid or carboxymethyl cellulose. The enteric-soluble polymer may be among others methyl acrylate/methacrylic acid copolymers and methyl methacrylate/methacrylic acid copolymers.

Japanese Patent Application (Kokai) No. 62-263124 discloses a pravastatin formulation which includes one or more (1) low molecular weight acids, (2) polyanionic polymers, and (3) enteric macromolecules, but not containing both a polyanionic polymer and an enteric macromolecule. The low molecular weight acid may be phosphoric acid, fumaric acid, tartaric acid, citric acid, malic acid, succinic acid, phthalic acid and vitamin C. The enteric macromolecule may be among others methyl acrylate/methacrylic acid copolymers and methyl methacrylate/methacylic acid copolymers.

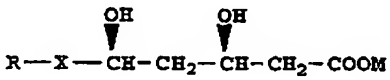
U.S. Patent Nos. 5,180, 589 and 5,030,447 to Joshi et al disclose pravastatin compositions which have good stability in an acidic environment and thus enhanced storage stability. The pravastatin compositions include a basifying agent (such as magnesium oxide, sodium hydroxide,

potassium hydroxide, lithium hydroxide, calcium hydroxide, magnesium hydroxide) to ensure acceptable storage stability, and may include a coating layer which includes one or more film-formers or binders such as hydroxypropylmethyl cellulose, ethyl cellulose, cellulose acetate and the like, and one or more plasticizers such as diethyl phthalate.

U.S. Patent No. 5,225,202 to Hodges et al discloses an enteric coated pharmaceutical composition which is formed of a core which includes a medicament which is sensitive to a low pH environment of less than 3 (such as pravastatin), a disintegrant or swelling agent, a buffering agent (such as magnesium oxide, calcium or magnesium hydroxide, as well as others) and an enteric coating surrounding the core which coating includes a neutralized form of hydroxypropylmethyl cellulose phthalate and plasticizers (such as diethyl phthalate, polyethylene glycol as well as others) and an anti-adherent (in the case of coating of pellets) such as talc.

In the "Background of the Invention" section, column 1, Hodges et al disclose enteric coatings employed in Mehta et al U.S. Pat. Nos. 4,728,512 and 4,794,001 (and not employed in the Hodges enteric coated pharmaceutical compositions) namely "neutral copolymer of polymethacrylic acid esters (Eudragit L30D) (F.W. Goodhart et al, Pharm. Tech., pp 64-71, April, 1984); copolymers of methacrylic acid and methacrylic acid methyl ester (Eudragits), or a neutral copolymer of polymethacrylic acid esters containing metallic stearates...."

U.S. Patent No. 5,356,896 to Kabadi et al discloses a pharmaceutical composition which contains an HMG CoA reductase inhibitor compound of the structure



where R is an organic radical

X is -CH=CH- and

M is a physiologically acceptable cation.

The Kabadi et al HMG CoA reductase inhibitor is preferably fluvastatin and does not include pravastatin.

In addition to the HMG CoA reductase inhibitor, the Kabadi et al composition contains an alkaline stabilizing medium capable of imparting a pH of at least 8 which include alkali metal hydroxides such as NaOH, KOH or LiOH, inorganic carbonate salts such as Na_2CO_3, K_2CO_3, $NaHCO_3$ as well as others.

The Kabadi et al composition may optionally include an enteric film coating such as "hydroxypropylmethyl cellulose phthalate, cellulose acetate phthalate, polyvinyl acetate phthalate, methyl cellulose phthalate, copolymerized methacrylic acid/methylacrylic acid methyl esters (e.g. Eudragit® Rohm America Incorporated)." (Column 5, lines 9 to 18). Kabadi et al teach that "the enteric coating is preferably applied to result in about a 5 to 12%, preferably 8 to 10%, weight increase of the capsule, pellet or tablet core."

Previous attempts to improve pravastatin bioavailability such as in U.S. Patent Nos. 4,661,162 and 5,225,202 have not produced desired results.

U.S. Patent No. 4,997,658 to Alberts et al discloses a method for enhancing the lowering of plasma cholesterol level by the time-controlled administration of an HMG CoA reductase inhibitor (which can include pravastatin) over a period of 6 to 24 hours employing diffusion controlled systems, osmotic devices, dissolution controlled matrices and erodible/degradable matrices. Alberts et al do not disclose any specific examples or formulations containing pravastatin.

Thus, a pravastatin formulation which decreases pravastatin exposure to the deleterious acidic environment of the stomach while enabling pravastatin to be absorbed in the small intestine to increase bioavailability and blood levels while enhancing LDl-C and triglyceride reduction would indeed fulfill a long felt want and would be a

significant advance in treatment of cholesterol related diseases.

Description of the Invention

In accordance with the present invention, an enteric coated pravastatin formulation is provided which includes a medicament which may degrade in a low pH environment but which is protected by the enteric coating from doing so. The pravastatin formulation of the invention, which is preferably in the form of beads or pellets, each bead of which includes a core which includes a medicament which is sensitive to a low pH environment, such as pravastatin, an optional buffering or basifying agent, and an enteric coating surrounding the core which coating will comprise at least about 17.5 grams of coating per m^2 surface area of the core beads (which is equivalent to about 5% w/w or more enteric coating for an average diameter core bead of 1.0 mm and an average weight of 0.78 mg), and preferably from about 20 to about 210 grams of coating per m^2 surface area of the core beads which is equivalent to about 5 to about 60% w/w enteric coating for an average diameter core bead of 1.0 mm and an average weight of 0.78 mg. More preferably, the enteric coating will comprise from about 35 to about 150 grams per m^2 surface area of the core beads which is equivalent to from about 10 to about 50% w/w enteric coating for an average diameter core bead of 1.0 mm and an average weight of 0.78 mg.

The above enteric coated pravastatin formulation will be free of polyanionic polymers, namely, alginic acid, polypectinic acid or carboxymethyl cellulose and salts thereof and low molecular weight acids, namely, phosphonic acid, fumaric acid, tartaric acid, citric acid, malic acid, succinic acid, phthalic acid and vitamin C.

It will be appreciated by those skilled in the art that corresponding and proportional levels of enteric coating will be employed with different size beads.

In addition, it will be understood that the formulation of the invention may be formed of beads contained in a single capsule or in two or more different capsules each containing beads of a different level of enteric coating and/or a different amount of pravastatin. It will also be understood where two or more capsules are required, the beads in each capsule may be the same or different insofar as enteric coating levels and/or amounts of pravastatin employed and/or size of beads.

In addition, in accordance with the present invention, a prolonged release enteric coated pravastatin formulation is provided which is in the form of a plurality of beads each of which includes an enteric coating which protects against pravastatin degradation in an acid environment as in the stomach while enabling release of pravastatin in the small intestine to be absorbed therein. In fact, it is believed that the pravastatin is absorbed throughout the small intestine, namely, in the duodenum, jejunum and ileum. The resulting prolonged release composition provides for improved bioavailability, increased blood levels and enhanced reduction in LDL-C cholesterol and triglycerides as compared to immediate release compositions which have the duodenum as the major absorption site.

The prolonged release enteric coated pravastatin formulation of the invention, which is in the form of a plurality of beads, particles, beadlets, granules or pellets, includes beads having a core which includes pravastatin which is sensitive to a low pH environment, optionally a buffering or basifying agent, and an enteric coating surrounding the core which coating will comprise at least about 17.5 grams of coating per m^2 surface area of the composition, (which is equivalent to 5% w/w or more enteric coating for an average diameter core bead of 1.0 mm and an average weight of 0.78 mg).

The prolonged release enteric coated pravastatin formulation of the invention will preferably comprise a

plurality of enteric coated beads (in the same capsule or in two or more capsules), the beads containing varying and different levels or amounts of enteric coating (that is a mixture of beads of the same or different bead size and containing different enteric coating levels or amounts), the mixture of beads being contained in the same capsule or divided up into two more capsules, to enable the beads to pass through the stomach while providing adequate protection against acid degradation, and pass into the small intestine wherein it allows for release of pravastatin throughout the small intestine, that is into the duodenum, jejunum and ileum from which the pravastatin is absorbed into the bloodstream.

It will be understood that the prolonged release enteric coated pravastatin formulation of the invention may comprise beads of different size containing the same level (%) of enteric coating to achieve release of pravastatin throughout the small intestine.

The enteric coating will include a methacrylic acid copolymer, preferably a copolymer of methacrylic acid and methacrylic acid methyl ester or a methylmethacrylate/ methacrylic acid copolymer. The enteric polymer may be partially neutralized. In addition, the formulation will include a hydrophobic plasticizer for the enteric coating material, such as diethyl phthalate, and an optional overcoating of an anti-adherent.

The novel enteric coated pravastatin formulation of the invention will provide for protection of pravastatin, at pH's less than 3 (such as found in the stomach) but will allow for prolonged slow drug release at a pH 4 or higher (such as found in the small intestine) over a period of less than 6 hours, and preferably over a period from about 1 to about 5 hours.

The ability of the enteric coat to prevent stomach acid migration to the core and/or prevent drug release from the core to the acidic environment of the stomach, and consequently prevent acid degradation of pravastatin, and

allow for and enable release of pravastatin for absorption in the small intestine, preferably substantially throughout the small intestine, is critical to achieving maximum improvement in bioavailability and blood levels and maximum improvement in LDL-C and triglyceride reduction. This is dependent upon levels of enteric coating, type of enteric polymer, and plasticizer used.

In addition, in accordance with the present invention, a method is provided for enhancing absorption properties of pravastatin in human patients, wherein the pravastatin in the form of a formulation comprising pravastatin, optionally a basifying agent and an enteric coating as described herein, (which preferably includes varying and different levels or amounts of enteric coating) is administered to a human patient in need of treatment, wherein due to the enteric coating, the absorption and/or bioavailability properties of the pravastatin are enhanced, preferably by at least about 75%, and more preferably by about 100%, to achieve enhanced human patient benefit including enhanced LDL- cholesterol lowering and triglyceride lowering and maximum benefits resulting from such cholesterol lowering and triglyceride lowering.

In addition, in accordance with the present invention, a method is provided for lowering serum cholesterol, preventing or inhibiting or treating atherosclerosis, and/or reducing risk of or treating a cardiovascular event or disease including coronary artery disease and cerebrovascular disease, in human patients, wherein a prolonged release pravastatin formulation comprised of a plurality of enteric coated pravastatin beads which preferably include a plurality beads of different levels of enteric coating, is administered to a human patient in need of treatment.

In a preferred embodiment, the enteric coated beads will be formed of a mixture of beads which include varying and different amounts of enteric coating so as to enable the beads to release pravastatin substantially throughout

the small intestine. Thus, for example, a 10 to 160 mg pravastatin dose may include one or more portions of beads containing from about 0 to about 50%, preferably from about 10 to about 40% by weight of the total bead formulation containing from about 17.5 to about 87.5 mg of enteric coating per m^2 surface area of bead, and/or one or more portions of beads containing from about 0 to about 60%, preferably from about 20 to about 50% by weight of the total bead formulation containing from about 105 to about 140 mg of enteric coating per m^2 surface area of bead, and/or one or more portions of beads containing from about 0 to about 60%, preferably from about 30 to about 50% by weight of the total bead formulation containing from about 140 to about 210 mg of enteric coating per m^2 surface area of bead. This translates to from about 5% to about 60% by weight enteric coating based on the weight of the final pravastatin bead dosage form (for example, average diameter of about 1 mm and weight of about 0.78 mg per bead). It should also be understood that the amount of pravastatin present in the beads may vary from portion to portion of beads making up the formulation. Furthermore, the number of different portions of beads making up the formulation may vary from one to seven or more, preferably two to four. It will also be understood that the present invention includes a mixture of two or more beads of different dimensions each of which may have the same enteric coating level. The beads of varying size, but having the same (or different) enteric coating levels, will achieve prolonged release of pravastatin.

Preferred pharmaceutical compositions of the present invention may take the form of several embodiments. Thus, in one embodiment of the invention, a pravastatin formulation is provided in the form of a plurality of beads which includes a pravastatin-containing core in the form of beads which optionally include a basifying agent as described above, and an enteric coating as described above surrounding the core. In an optional embodiment, the core

may include a protective coating under the enteric coat and an outer coating of an anti-adherent material. The beads may be loaded into capsules for dosing.

The above enteric coated formulations of the invention may be employed in admixture or combination with known pravastatin formulations including immediate release formulations including the commercially available Pravachol® formulation.

Detailed Description of the Invention

The pharmaceutical composition of the invention which includes a core containing pravastatin and an optional basifying agent, and an enteric overcoat as described herein, is effective in preventing, reducing and/or treating elevated cholesterol levels (such as in hypercholesterolemia); atherosclerosis, cardiovascular events and disease including coronary events and cerebrovascular events, and coronary artery disease and/or cerebrovascular disease, and hypertriglyceridemia.

The terms "cardiovascular event(s)" and "cardiovascular disease" as employed herein refer to coronary and/or cerebrovascular event(s) and disease including primary myocardial infarction, secondary myocardial infarction, myocardial ischemia, angina pectoris (including unstable angina), congestive heart failure, sudden cardiac death, cerebral infarction, cerebral thrombosis, cerebral ischemia, transient ischemic attack and the like.

The term "coronary artery disease" (CAD) as employed herein refers to diseases including atherosclerosis of the coronary arteries, previous myocardial infarction, ischemia, angina pectoris and/or heart failure.

The term "cerebrovascular disease" as employed herein refers to diseases including atherosclerosis of the intracranial and/or extracranial arteries, cerebral infarction, cerebral thrombosis, cerebral ischemia, stroke, and/or transient ischemic attacks.

The term "absorbed substantially throughout the small intestine" refers to the ability of pravastatin to be absorbed not only in the duodenum but down to the jejunum and the ileum where substantial amounts of pravastatin are absorbed as well.

The term "mixture of beads containing different levels of enteric coating" refers to the fact that the pravastatin bead formulation of the invention includes a mixture of beads, which may be the same or different sizes, preferably the same size, prescribed portions of which are coated with prescribed levels of enteric coating (preferably different levels of enteric coating) to enable beads to be released and absorbed throughout the small intestine, that is in the duodenum, jejunum and ileum, and not primarily in the duodenum as in the case of immediate release pravastatin formulations. The various portions of beads containing different enteric coating levels may also contain different amounts of pravastatin.

The term "enhanced absorption and/or bioavailability properties" of pravastatin refers to the ability of the pravastatin to be absorbed into the blood stream of a human patient by delivering it to the desired site, namely the small intestine.

The terms "particles", "granules", "pellets", "beadlets", and "beads" of pravastatin are used interchangeably, and will preferably have from about 0.1 to about 10 mm diameter.

The term "pravastatin" as employed herein encompasses pravastatin and all salts such as the sodium salt, and all forms thereof including the lactone.

In preparing the above described oral formulations, granules or beads of pravastatin can be incorporated into the formulation. In many cases, discrete granules of pravastatin are needed so that these can be coated with a protective coating layer. The process of making pravastatin granules may be common to most of the formulations. The granules or beads may be prepared in

different ways and used in any of the above formulations depending on the specific needs and limitations of the formulation. Some of the processes which can be used for preparing granule formulations are described below.

(a) The granules or beads of pravastatin cholesterol lowering agent can be formed by dry compacting the pravastatin as is or after blending with a basifying agent (such as magnesium oxide or calcium carbonate) and a lubricant, such as zinc stearate, magnesium stearate, calcium stearate, talc, carnauba wax, or hydrogenated vegetable oils and/or fats, in an amount within the range from about 0.01 to about 4%, and preferably from about 0.1 to about 2%. Optionally, suitable bulking agents and/or fillers and/or binders can be added, as described hereinafter.

The compacts can be prepared by roller compaction or slugging. By this process, granules of almost 100% drug load can be prepared. Lower drug load granules may be prepared by employing additional fillers and excipients in the blend used for compaction. The compacts can be broken into granules with suitable equipment. The resulting granules can be sized and the desired size fraction can be separated and collected with the rest being recycled.

(b) Spherical and very high drug load granules or beads of pravastatin can be prepared by simple wet granulation or micro-granulation of pravastatin powder in a high shear granulator using water. Sufficient water is added to enable preparation of small spherical granules (that is, average particles size of less than about 1mm). The resulting granules can be sized and screened to collect desired size fraction, and dried to desired moisture level. As indicated, basifying agent will be included in the formulation. The under and over sized fractions can be recycled. If less than 100% drug load is desired, fillers and excipients can be included in the powder to be micro granulated.

(c) In another embodiment of the above method, pravastatin granules or beads can be prepared using Moisture Activated Dry Granulation (MADG) process. In this case, a portion (30-60%) of the pravastatin core can be granulated as above using all of the moisture needed for the whole blend to form agglomerates and then the remaining pravastatin added, and the mixture blended to prepare the granules. The final blend can be sized, screened, and desired size fraction removed with over and under size to be recycled if necessary. In this process, since normally, drying is not involved, minimum quantities of moisture will be used as compared to process (b). However, for stability reasons, the granules so prepared can still be dried.

(d) In yet another embodiment of the above method, conventional wet granules of the pravastatin as in process (b) can be prepared by first making a wet mass using conventional wet massing equipment. The wet mass can be sized wet and dried or dried as is and then broken into granules, which are screened and the desired size fraction is collected.

(e) In still another embodiment of the above method, the wet mass prepared in method (d) can be extruded. The extrudate can be dried, broken into granules, and sieved to collect desired size fraction. This process can produce high (>90%) drug load, dense and hard particles.

(f) In yet another embodiment of the above method, more uniform and spherical particles can be prepared by employing conventional spheronization processes. This will require use of higher level of excipients to allow proper extrusion of the wet mass and trouble free spheronization of the extrudate. Depending on the selection of the excipients and modification of the spheronization process, it may require 5 to 99% excipients. For this purpose, pravastatin is blended with microcrystalline cellulose and with a small amount (0.5-5%) of basifying agent such as magnesium oxide, calcium carbonate or magnesium hydroxide,

to insure chemical stability. The blend is then wet massed and extruded. The extrudate is then spheronized to prepare the beads. These beads are dried in a hot air tray oven or fluid bed dryer. The beads can be further sized to remove under and over sized particles. While microcrystalline cellulose is preferred for bead formation, other excipients, for example, starch, lactose, starch 1500, silicified microcrystalline cellulose and the like, or any combination of these may be used as well.

(g) In yet another embodiment of this method, a much higher drug concentration bead can be prepared by saving a portion of the drug blend before wet massing and using this dry powder to dust while spheronizing.

The pravastatin formulation of the invention in the form of a plurality of enteric coated pravastatin granules, particles, beadlets, beads, or cylindrical particles, may be prepared by first forming pravastatin granules, particles, beads or cylindrical particles (hereinafter "granules") employing any of the granulation processes described above, preferably process (f) for beads or process (e) for granules. These granules which will have an average particle size within the range from about 200 μm to about 2000 μm, can be coated with an optional protective coat, for example, employing a coating polymer such as a 2-10% basified solution of polyvinyl pyrrolidone (PVP), a 2-20% solution of hydroxypropylmethyl cellulose (HPMC), or Opadry Clear (HPMC), or a 10-30% suspension of neutralized Eudragit L-30-D55 (acrylic acid copolymers-Rohm America Incorporated) (about 30% solids) containing 10 to 40% diethyl phthalate (W/W) or Citroflex® as plasticizer. A 0.5 to 10% protective coating may be applied in a fluid bed particle coating system or a coating pan.

The pravastatin beads optionally containing basifying agent with or without the protective coating are enteric coated. The enteric coated beads can be further coated with an anti-adherent coating. These beads can be dosed as granules or beads or in the form of capsules after

encapsulation. Upon ingestion, the beads will pass through the stomach as intact beads due to the enteric coat. As the beads reach the duodenum, jejunum and ileum, the enteric coat will dissolve followed by dissolution of the pravastatin particles and absorption thereby into the duodenum, jejunum and ileum.

The pravastatin formulation of the invention will contain pravastatin in an amount within the range from about 1 to about 90% by weight of the formulation. In practice, the amount of pravastatin normally employed will be exemplified in the 53nd edition of the Physician's Desk Reference (PDR) (1999). Thus, depending upon the particular statin, it may be employed in amounts within the range from about 0.1 mg to 2000 mg per day in single or divided doses, and preferably from about 0.2 to about 400 mg per day. Most preferably for pravastatin, a daily dosage of 5 to 160 mg may be employed.

The basifying agent will optionally be incorporated into the granules prepared by means of processes (a) to (g) employing conventional procedures as described in the working Examples. The basifying agent will be included to aid in minimizing drug degradation in the core due to acid ingress in low pH environments as well as to increase the shelf life of the product. The basifying agent will be present in an amount within the range of from about 0.1 to about 15% by weight and preferably from about 0.5 to about 10% by weight of the composition. Examples of basifying agents which may be included herein include, but are not limited to, sodium acetate, sodium citrate, sodium tartrate, sodium fumarate, sodium malate, sodium succinate, calcium carbonate, sodium carbonate, potassium carbonate, sodium bicarbonate, dihydroxy aluminum sodium carbonate, magnesium oxide, aluminum oxide, an alkali metal hydroxide such as sodium hydroxide, potassium hydroxide or lithium hydroxide or an alkaline earth metal hydroxide such as calcium hydroxide or magnesium hydroxide, with magnesium oxide or calcium carbonate being preferred.

The formulation of the invention will also include one or more fillers or excipients in an amount within the range of from about 0 to about 90% by weight and preferably from about 5 to about 80% by weight such as lactose, sugar, corn starch, modified corn starch, mannitol, sorbitol, inorganic salts such as calcium carbonate, calcium phosphate, and/or cellulose derivatives such as wood cellulose, hydroxypropylmethyl cellulose (HPMC), and microcrystalline cellulose.

One or more binders will be present in addition to or in lieu of the fillers in an amount within the range of from about 0 to about 35% and preferably from about 1 to about 30% by weight of the composition. Examples of such binders which are suitable for use herein include basified polyvinylpyrrolidone (molecular weight ranging from about 5000 to about 80,000 and preferably about 40,000), lactose, HPMC, starches such as corn starch, modified corn starch, sugars, gum acacia and the like as well as a wax binder in finely powdered form (less than 500 microns) such as carnauba wax, paraffin, spermaceti, polyethylenes or microcrystalline wax.

The enteric coating will be present in varying and different levels as described hereinbefore to impart the desired properties to such formulation, namely, improved bioavailability and efficacy (in lowering LDL cholesterol) and triglycerides. The enteric coating will be methacrylic acid copolymer (Eudragit L30D-Rohm America Incorporated), and preferably a copolymer of methacrylic acid and methacrylic acid ester or a copolymer of methylmethacrylate/methacrylic acid, which will be present in an amount from about 70 to about 95% by weight of the enteric coating. The enteric polymer may be partially neutralized.

The enteric coating will include a plasticizer preferably a hydrophobic plasticizer in an amount from about 5 to 30%, preferably from about 0.5 to about 6% by weight of the enteric coating. Examples of plasticizers

include diethyl phthalate, tributyl citrate, triacetin, dibutyl phthalate, dibutyl sebacate, or Myvacet 940 (acetylated monoglycerides) and other commonly used plasticizers as may be suitable for the enteric polymer employed herein. It will be appreciated that the enteric polymer with suitable plasticizer can be used in aqueous or non-aqueous system to form an enteric coating on the pravastatin bead or granule.

Preferred enteric coating polymer is Eudragit L-30-D55 with diethyl phthalate as a plasticizer. At least 35 grams of the coating solution per m^2 surface area would be sufficient to provide a coat with enteric qualities when applied from an aqueous system.

To form the enteric coating, a 10-30% suspension of Eudragit® L-30-D55, preferably 15 to 20% containing 1 to 5% diethyl phthalate, preferably 1.5-3.0% is prepared in purified water. The uncoated or protective-coated cores or beads are enteric coated with this suspension in a fluid bed coater fitted with a Wurster column or top coating capability or a pan-coater.

The above enteric coated granules are further coated with an anti-adherent material. Talc, magnesium stearate, calcium stearate, silica gel, titanium dioxide and the like may be used. The anti-adherent material, preferably talc, is used at 0.1-5% level and preferably 0.2 to 2.0%. Coated particles and talc may be loaded into a tumbling type blender and blended for 5-30 minutes.

The above coated particles can be encapsulated into hard gelatin capsules for the desired potency.

A preferred enteric coated pravastatin formulation of the invention in the form of a bead is set out below.

Material	Possible Range %	Preferred Range %
Core		
Pravastatin Sodium	1 to 90	5 to 80
Basifying Agent (such as MgO or $CaCO_3$	0.1 to 15_	0.5 to 10_
Filler such as Microcrystalline cellulose	10 to 99	20 to 95
	g/m^2 Surface Area of Core	
	Possible Range%	Preferred Range%
Optional Subcoat	(0 to 35)	(1.8 to 17.5)
Film polymer such as Methocel E3 (HPMC)	0 to 35	1.8 to 17.5
Enteric Overcoat	(17.5 to 210)	(35 to 140)
Polymethacrylic acid esters such as EUDRAGIT LD30 (dry weight basis)	15.2 to 161.5	30.4 to 121.7
Diethyl phthalate	2.3 to 48.5_	4.6 to 18.3_
Dusting Talc	0 to 5	0.1 to 2.0

The enteric coat and the optional subcoat are based on the surface area of the core beads. As indicated hereinbefore, for a single core bead of approximately 0.78 mg and 1 mm in diameter, the possible range of the enteric coat is from about 5% to about 60% and the preferred range is from about 15% to about 40% based on the weight of the core and the enteric coat, respectively. For a core bead of similar weight and dimension, the possible range of the subcoat is from about 0% to about 10% and the preferred range is from about 0.5% to about 5.0% based on the weight of the core, the optional subcoat, and the enteric coat, respectively.

The enteric coated pharmaceutical composition in the form of pellets or beadlets may also be prepared employing an extrusion-spheronization procedure such as described in U.S. Patent No. 4,808,413 to Joshi et al. For example, the pharmaceutical (preferably pravastatin) is dissolved in a granulation liquid (water). The fillers, binders, disintegrants and buffering agent (for example, microcrystalline cellulose, lactose, sodium starch glycolate, polyvinylpyrollidone and sodium citrate) are thoroughly mixed, for example, using a conventional mixer such as a planetary mixer, to form a dry blend. The dry blend is then granulated using the above granulation solution and continued to the endpoint with water. The wet mass is extruded, for example, employing a Nica, Luwa or other type of extruders to form an extrudate which is then passed through spheronizing equipment, such as Nica, Caleva or other type, which converts the extrudate into beadlets of appropriate particle size range. The beadlets may then be dried by tray drying oven or fluid bed drying. Where the core is to be a tablet, the tablet may be formed using conventional techniques.

The dried beadlets or pellets, may then be coated with a subcoat, for example, with a solution of hydroxypropylmethyl cellulose (Pharmacoat 603) and polyethylene glycol 400. These sub-coated beadlets or pellets are then overcoated with the enteric coating composition which is a dispersion of a copolymer of polymethacrylic acid esters and a plasticizer preferably diethyl phthalate.

The so-formed pellets or beadlets may be filled into hard gelatin capsules.

In carrying out the method of the present invention, the pravastatin bead formulation of the invention may be administered to mammalian species, such as monkeys, dogs, cats, rats, humans, etc., and, as described hereinbefore, may be incorporated in a capsule. The above dosage forms may also include antibacterial, anti-oxidants such as

Vitamin C and Vitamin E, as well as Vitamin B_6, Vitamin B_{12}, folic acid, sodium bisulfite, and the like.

The dose administered must be adjusted according to age, weight and condition of the patient, as well as the route of administration, dosage form and regimen and the desired result.

The formulations described above may be administered in the dosage forms as described above in single or divided doses of one to four times daily. It may be advisable to start a patient on a low dose combination and work up gradually to a high dose combination.

Such dosage forms can be administered to the patient on a regimen of one to four doses per day.

As indicated, pravastatin forms commonly known pharmaceutically acceptable salts such as alkali metal and other common basic salts or acid addition salts, etc. References to the base substances are therefore intended to include those common salts known to be substantially equivalent to the parent compound.

The formulations as described above will be administered for a prolonged period, that is, for as long as the potential for atherosclerosis, cardiovascular events and disease including coronary artery disease and/or cerebrovascular disease remains or the symptoms continue. Sustained release forms of such formulations which may provide such amounts daily, biweekly, weekly, monthly and the like may also be employed. A dosing period of at least 10 days are required to achieve minimal benefit.

The following Examples represent preferred embodiments of the present invention.

Formulations suitable for oral administration are prepared as described below.

Example

A pravastatin capsule formulation which includes granules or beads of pravastatin sodium, MgO or $CaCO_3$ basifying agent, filler-binder, and Eudragit L-30-D55 enteric coating having the following composition is prepared as described below.

Formula for Capsule Formulation:

Uncoated Pravastatin Beads	1 - 90% drug load
(Basifying agent MgO or $CaCO_3$)	(0.5 to 1.0%)
Optional Protective Coating	
Uncoated Pravastatin Beads	90 to 100 mg
HPMC 0 to 10 mg	
Purified Water	q.s.
Enteric Coating	
Uncoated Pravastatin Beads or	
Protective Coated Pravastatin Beads	100 mg
Eudragit L-30-D55 (Dry Weight Basis)	4.6 to 130.4 mg
Diethyl Phthalate	0.7 to 29.6 mg
Purified Water	q.s.
Anti-adherent Coating	
Enteric Coated Beads	99.9 to 96 mg
Talc 0.1 to 4 mg	

Procedure:

A multi-step process is employed which starts with the preparation of pravastatin sodium granules. The granules can be prepared by any of the methods (a)-(f) described above, but methods (e) and (f) are preferred. These granules (having an average particle size ranging from about 710 µm to about 1700 µm) may optionally be coated with a protective coat. The protective coating polymer may be a 2-10% solution of basified PVP, or 2-20% solution of HPMC or Opadry® Clear with or without a

suitable plasticizer such as polyethylene glycol. A 0.5-10% coating can be applied in a fluid bed particle coating system. Among these, a preferred protective coating will be formed of 1-20% HPMC. The beads or particles are coated to 0.5-10% coat level in fluid bed apparatus with or without a Wurster insert or in a pan coater.

The above granules are coated as described above. These are coated with enteric coating polymers as follows. A 10-30% suspension of Eudragit L-30-D 55, preferably 15 to 20%, containing 1 to 6% diethyl phthalate preferably 1.5 to 4.5%, is prepared in purified water. The uncoated or protective coated beads are enteric coated with this suspension in a fluid bed coater fitted with or without a Wurster column or in a pan coater. A 15% to 60% weight gain would be sufficient to provide coat with enteric qualities.

The above enteric coated granules are further coated with anti-adherent material such as talc, magnesium stearate, calcium stearate, silica gel or titanium dioxide. Preferably talc is used as anti-adherent at 0.1 to 4% level, preferably 0.5 to 2%. Enteric coated granules and talc are loaded into a tumbling type blender and blended for 5 to 30 minutes, preferably 10 minutes.

The above coated granules are encapsulated into capsule hard shells suitable for the desired potency or compressed into a tablet matrix using a cushioning filler-binder system to provide a dosage form with 5 to 160 mg drug potency.

The resulting pravastatin sodium formulation will provide for improved absorption and/or bioavailability in human patients by at least about 75-100% over a similar formulation which does not contain the enteric coating as defined above. When the beads with different coating levels are mixed, these provide a prolonged release formulation.

SPECIFIC EXAMPLES OF PRAVASTATIN FORMULATION OF THE INVENTION

Formulations 1-11 are specific preferred examples of enteric coated pravastatin beads filled in a capsule. Formulations 1-5 and 8 are intended to deliver 40 mg pravastatin sodium. Formulations 6, 7 and 9 are intended to deliver 20 mg. Formulation 10 is intended to deliver 80 mg, and Formulation 11 is intended to deliver 160 mg. Thus, a dose range of 2-160 mg is easily achievable using these Examples. The beads of Formulations 1-6 and 8-11 are composed of pravastatin sodium, magnesium oxide as basifying agent, and microcrystalline cellulose coated with different levels of the enteric polymer Eudragit® L30D plasticized with diethyl phthalate and dusted with talc prior to filling in capsules. The % of pravastatin in the core beads for Formulations 1-4, 6, 7 and 9 is 10%, whereas those of Formulations 5, 10 and 11 are 20%, 40% and 80%, respectively. The coated beads are resistant to the acid degradation in the stomach but release the pravastatin at pH greater than 4. The coating levels presented in these examples are 15%, 20%, 25%, 30% and 40% w/w which for an average diameter core bead of 1.0 mm and an average weight of 0.78 mg, represents a 52.5, 70, 87.5, 105, and 140 gram of enteric coating per m^2 surface area of the core beads. Beads with different coating levels should release the drug at different portions of the gastrointestinal tract. Thus, beads having higher coating levels would release at a later time. Different fractions of beads with different levels of coating can be mixed to achieve desired release rate for optimum bioavailability and efficacy. The difference between Formulations 1,2,3,4,6 and 8 is in the level of the enteric coating applied to the beads as well as the fraction of each enteric coated beads present. Thus, Formulation 1 contains 40 mg pravastatin loaded beads coated at 15% level. Formulation 2 contains 20 mg pravastatin coated at 15% coating, 12 mg pravastatin coated

at 25% coating and 8 mg pravastatin coated at 40% coating levels. Formulation 3 contains 10 mg immediate release pravastatin in the form of Pravachol® 10 mg tablet, 10 mg pravastatin coated at 15% coating, 10 mg pravastatin coated at 25% coating and 10 mg pravastatin coated at 40% coating. Formulation 4 contains 10 mg pravastatin coated at 15% coating, 12 mg pravastatin coated at 25% coating and 18 mg pravastatin coated at 40% coating. Formulation 5 contains 40 mg pravastatin coated at 30% coating. Formulation 7 is similar to Formulation 6, except that it contains calcium carbonate as the basifying agent instead of magnesium oxide. Formulation 8 contains 20 mg pravastatin coated at 20% coating and 20 mg pravastatin at 40% coating. Formulation 9 contains a hydroxypropyl methylcellulose subcoat to separate the acid-sensitive drug pravastatin sodium from the acidic enteric coating polymer (Eudragit® L30D). Formulation 10 contains 80 mg pravastatin coated at 30% coating. Formulation 11 contains 160 mg pravastatin at 40% coating level. Formulation 12 contains 40 mg pravastatin coated at 40% coating level.

FORMULATION 1

Preparation of Core Beads (Pravastatin Sodium Beads for Capsules, 10% w/w):

a. Composition of Core Beads

Ingredient	Amount Per g
Pravastatin Sodium	0.100 g[A]
Magnesium Oxide, NF	0.005 g
Microcrystalline Cellulose, NF	ca. 0.895 g[B]
Purified Water, USP	q.s.[C]
Total Weight	1.000 g

A. This amount is based on the amount of pravastatin sodium at 100% potency. The exact amount will vary depending on the chemical purity ("as is" potency) of the pravastatin sodium.

B. The amount of microcrystalline cellulose will vary depending on the chemical purity of the pravastatin sodium used.

C. Purified water is used for processing only and is removed during drying. The preferred amount is 0.890 g. The range is 0.850 g to 0.950 g.

b. Procedure for Preparing Core Beads

1. Weigh the pravastatin sodium, magnesium oxide, and microcrystalline cellulose, and screen the ingredients, if necessary.
2. Blend the ingredients from Step 1.
3. Wet granulate the blend from Step 2 with purified water.
4. Extrude the wet mass from Step 3.
5. Spheronize the extrudate from Step 4.
6. Dry the beads from Step 5.
7. Screen the beads from Step 6 to obtain the appropriately sized fraction.

Enteric Coating of the Core Beads to 15% Polymer Level: (Pravastatin Sodium Modified Release Film Coated Beads for Capsules, 8.5% w/w):

a. Composition of Enteric Coated Beads

A. BEADS:

Ingredient	Amount Per g
Pravastatin Sodium Beads for Capsules, 10% w/w	0.845 g
Total Uncoated Beads Weight	0.845 g

B. FILM COAT:

Ingredient	Amount Per g
Eudragit L30D-55, NF (Dry Weight)	0.130 g
Diethyl Phthalate, NF	0.020 g
Total Weight of the Film Coat	0.150 g

C. DUSTING:

Ingredient	Amount Per g
Talc, USP	0.005 g
Total Weight of the Film Coated Beads	1.000 g

b. Procedure for Enteric Coating of Core Beads:

ENTERIC COATING SUSPENSION PREPARATION:

1. Filter the Eudragit L30D-55 suspension.
2. Weigh the Eudragit L30D-55 suspension from Step 1.
3. Weigh and slowly add the Diethyl Phthalate to the filtered Eudragit L30D-55 suspension from Step 2 and mix. Adjust suspension pH if desired by partially neutralizing the polymer to the desired pH.
4. Weigh and add the required amount of Water for Injection to the Eudragit L30D-55 and Diethyl Phthalate mixture from Step 3 and mix.

BEAD COATING:

- Weigh the Pravastatin Sodium Beads for Capsules, 10% w/w
- Film coat the Pravastatin Sodium Beads for Capsules, 10% w/w with the coating suspension using a fluid bed processor.
- Dry the coated beads.

DUSTING OF THE ENTERIC COATED BEADS:

- Dust the coated beads with talc in a tumbling mixer.

Filling of Enteric Coated Beads in Capsules

Ingredient	Amount Per Capsule
Pravastatin Sodium Modified Release Enteric Coated Beads for Capsules, 8.5% w/w	472.9 mg
White, Opaque, Size #0 Capsule Shell	One Capsule

FORMULATION 2

Preparation of Pravastatin Sodium Beads Containing 15% Enteric Coating, 25% Enteric Coating, and 40% Enteric Coating

Preparation of Core Beads (Pravastatin Sodium Beads for Capsules, 10% w/w)
As in Formulation 1

Enteric Coating of the Core Beads to 15% Polymer Level: (Pravastatin Sodium Modified Release Film Coated Beads for Capsules, 8.5% w/w)
As in Formulation 1

Enteric Coating of the Core Beads to 25% Polymer Level: (Pravastatin Sodium Modified Release Film Coated Beads for Capsules, 7.5% w/w):

a. Composition:

A. BEADS:

Ingredient	Amount Per g
Pravastatin Sodium Beads for Capsules, 10% w/w	0.746 g
Total Uncoated Beads Weight	0.746 g

B. ENTERIC COAT:

Ingredient	Amount Per g
Eudragit L30D-55, NF (Dry Weight)	0.216 g
Diethyl Phthalate, NF	0.032 g
Total Weight of the Enteric Coat	0.249 g

C. DUSTING:

Ingredient	Amount Per g
Talc, USP	0.005 g
Total Weight of the Enteric Coated Beads	1.000 g

b. Procedure:

Same as Formulation 1, Step IIb.

Enteric Coating of the Core Beads to 40% Polymer Level: (Pravastatin Sodium Modified Release Enteric Coated Beads for Capsules, 6.0% w/w):

a. Composition:

A. BEADS:

Ingredient	Amount Per g
Pravastatin Sodium Beads for Capsules, 10% w/w	0.597 g
Total Uncoated Beads Weight	0.597 g

B. ENTERIC COAT:

Ingredient	Amount Per g
Eudragit L30D-55, NF (Dry Weight)	0.346 g
Diethyl Phthalate, NF	0.052 g
Total Weight of the Enteric Coat	0.398 g

C. DUSTING:

Ingredient	Amount Per g
Talc, USP	0.005 g
Total Weight of the Enteric Coated Beads	1.000 g

b. Procedure:

Same as Formulation 1

Filling of Enteric Coated Beads in Capsules

Ingredient	Amount Per Two Capsules
Pravastatin Sodium Modified Release Enteric Coated Beads for Capsules, 8.5% w/w (15% enteric coating)	236.5 mg
Pravastatin Sodium Modified Release Enteric Coated Beads for Capsules, 7.5% w/w (25% enteric coating)	160.8 mg
Pravastatin Sodium Modified Release Enteric Coated Beads for Capsules, 6% w/w (40% enteric coating)	134.0 mg
White, Opaque, Size #0 Capsule Shell	Two Capsules

FORMULATION 3

Preparation of the Core Beads (Pravastatin Sodium Beads for Capsules, 10% w/w)

As in Formulation 1

Enteric Coating of the Core Beads to 15% Polymer Level: (Pravastatin Sodium Modified Release Enteric Coated Beads for Capsules, 8.5% w/w)

As in Formulation 1

Enteric Coating of the Core Beads to 25% Polymer Level: (Pravastatin Sodium Modified Release Enteric Coated Beads for Capsules, 7.5% w/w)
As in Formulation 2

Enteric Coating of the Core Beads to 40% Polymer Level: (Pravastatin Sodium Modified Release Enteric Coated Beads for Capsules, 6.0% w/w):
As in Formulation 2

Filling of Enteric Coated Beads in Capsules

Ingredient	Amount Per Two Capsules
Pravastatin Sodium (PRAVACHOL®) Tablet, 10 mg*	One Tablet
Pravastatin Sodium Modified Release Enteric Coated Beads for Capsules, 8.5% w/w	118.2 mg
Pravastatin Sodium Modified Release Enteric Coated Beads for Capsules, 7.5% w/w	134.0 mg
Pravastatin Sodium Modified Release Enteric Coated Beads for Capsules, 6% w/w	167.5 mg
White, Opaque, Size #0 Capsule Shell	Two Capsules

*10 mg pravastatin in the form of Pravachol® 10 mg tablet is used to provide an immediate release component.

FORMULATION 4

Preparation of the Core Beads (Pravastatin Sodium Beads for Capsules, 10% w/w)

As in Formulation 1

Enteric Coating of the Core Beads to 15% Polymer Level: (Pravastatin Sodium Modified Release Enteric Coated Beads for Capsules, 8.5% w/w)

As in Formulation 1

Enteric Coating of the Core Beads to 25% Polymer Level: (Pravastatin Sodium Modified Release Enteric Coated Beads for Capsules, 7.5% w/w)

As in Formulation 2

Enteric Coating of the Core Beads to 40% Polymer Level: (Pravastatin Sodium Modified Release Enteric Coated Beads for Capsules, 6.0% w/w):

As in Formulation 2

Filling of Enteric Coated Beads in Capsules

Ingredient	Amount Per Two Capsules
Pravastatin Sodium Modified Release Enteric Coated Beads for Capsules, 8.5% w/w	118.2 mg
Pravastatin Sodium Modified Release Enteric Coated Beads for Capsules, 7.5% w/w	160.8 mg
Pravastatin Sodium Modified Release Enteric Coated Beads for Capsules, 6% w/w	301.5 mg
White, Opaque, Size #0 Capsule Shell	Two Capsules

FORMULATION 5

a. Composition of Core Beads

Ingredient	Amount Per g
Pravastatin Sodium	0.2000 Kg[A]
Magnesium Oxide, NF	0.0050 Kg
Yellow Ferric Oxide, NF	0.0010 Kg
Microcrystalline Cellulose, NF	ca. 0.7940 Kg[B]
Purified Water, USP	q.s.[C]
Total Weight	1.0000 Kg

[A] This amount is based on the amount of pravastatin sodium at 100% potency. The exact amount will vary depending on the chemical purity ("as is" potency) of the pravastatin sodium.

[B] The amount of microcrystalline cellulose will vary depending on the chemical purity of the pravastatin sodium used.

[C] Purified Water is used for processing only and is removed during drying. The preferred amount is 0.7640 Kg. The range is 0.7500 Kg to 0.7780 Kg.

b. Procedure for Preparing Core Beads

1. Weigh the pravastatin sodium, magnesium oxide, yellow ferric oxide, and microcrystalline cellulose, and screen the ingredients, if necessary.
2. Blend the ingredients from Step 1.
3. Wet granulate the blend from Step 2 with purified water.
4. Extrude the wet mass from Step 3.
5. Spheronize the extrudate from Step 4.
6. Dry the beads from Step 5.
7. Screen the beads from Step 6 to obtain the appropriately sized fraction.

Enteric Coating of the Core Beads to 30% Polymer Level: (Pravastatin Sodium Modified Release Film Coated Beads for Capsules, 14% w/w):

a. Composition of Enteric Coated Beads

A. BEADS:

Ingredient	Amount Per Kg
Pravastatin Sodium Beads for Capsules, 20% w/w	0.6965 Kg
Total Uncoated Beads Weight	0.6965 Kg

B. FILM COAT:

Ingredient	Amount Per Kg
Eudragit L30D-55, NF (Dry Weight)	0.2596 Kg
Diethyl Phthalate, NF	0.0389 Kg
Total Weight of the Film Coat	0.2985 Kg

C. DUSTING:

Ingredient	Amount Per Kg
Talc, USP	0.0050 Kg
Total Weight of the Film Coated Beads	1.0000 Kg

b. Procedure for Enteric Coating of Core Beads:

ENTERIC COATING SUSPENSION PREPARATION:

1. Filter the Eudragit L30D-55 suspension.
2. Weigh the Eudragit L30D-55 suspension from Step 1.
3. Weigh and slowly add the Diethyl Phthalate to the filtered Eudragit L30D-55 suspension from Step 2 and mix.

BEAD COATING:

- Weigh the "Pravastatin Sodium Beads for Capsules, 20% w/w.

- Film coat the "Pravastatin Sodium Beads for Capsules, 20% w/w", with the coating suspension from using a fluid bed processor.
- Dry the coated beads.

DUSTING OF THE COATED BEADS:

- Dust the coated beads with talc in a tumbling mixer.

FILLING OF ENTERIC COATED BEADS IN CAPSULES
(40 mg Strength)

Ingredient	Amount Per Capsule
Pravastatin Sodium Modified Release Film Coated Beads for Capsules, 14% w/w	287.2 mg
White, Opaque, Size #1 Capsule Shell	One Capsule

FORMULATION 6

Preparation of the Core Beads (Pravastatin Sodium Beads for Capsules, 10% w/w)
Same as Formulation 1.

Enteric Coating of the Core Beads to 30% Polymer Level: (Pravastatin Sodium Modified Release Enteric Coated Beads for Capsules, 7.0% w/w):

a. Composition:

A. BEADS:

Ingredient	Amount Per g
Pravastatin Sodium Beads for Capsules, 10% w/w	0.695 g
Total Uncoated Beads Weight	0.695 g

B. ENTERIC COAT:

Ingredient	Amount Per g
Eudragit L30D-55, NF (Dry Weight)	0.261 g
Diethyl Phthalate, NF	0.039 g
Total Weight of the Film Coat	0.300 g

C. DUSTING:

Ingredient	Amount Per g
Talc, USP	0.005 g
Total Weight of the Enteric Coated Beads	1.000 g

b. Procedure:

ENTERIC COATING SUSPENSION PREPARATION:

1. Weigh the Eudragit L30D-55 suspension.
2. Filter the Eudragit L30D-55 suspension from Step 1.
3. Weigh and slowly add the Diethyl Phthalate to the filtered Eudragit L30D-55 suspension from Step 2 and mix.
4. Weigh and add the required amount of purified water to the Eudragit L30D-55 and Diethyl Phthalate mixture from Step 3 and mix.

BEAD COATING:

- Weigh the Pravastatin Sodium Beads for Capsules, 10% w/w
- Film coat the Pravastatin Sodium Beads for Capsules, 10% w/w with the enteric coating suspension using a fluid bed processor.
- Dry the coated beads.

DUSTING OF THE ENTERIC COATED BEADS:

- Dust the coated beads with talc in a tumbling mixer.

Filling of Enteric Coated Beads in Capsules

Ingredient	Amount Per Capsule
Pravastatin Sodium Modified Release Film Coated Beads for Capsules, 7.0% w/w	287.2 mg
White, Opaque, Size #1 Capsule Shell	One Capsule

FORMULATION 7

Preparation of the Core Beads (Pravastatin Sodium Beads for Capsules, 10% w/w):

a. Composition:

Ingredient	Amount Per g
Pravastatin Sodium	0.100 g[A]
Calcium Carbonate, NF	0.010 g
Microcrystalline Cellulose, NF ca.	0.890 g[B]
Purified Water	q.s.[C]
Total Weight	1.000 g

A This amount is based on the amount of pravastatin sodium at 100% potency. The exact amount will vary depending on the chemical purity ("as is" potency) of the pravastatin sodium.

B The amount of microcrystalline cellulose will vary depending on the chemical purity of the pravastatin sodium used.

C Purified water is used for processing only and is removed during drying. The preferred amount is 0.8900 g. The range is 0.8500 g to 0.9500 g.

b. Procedure:

1. Weigh the pravastatin sodium, calcium carbonate, and microcrystalline cellulose, and screen the ingredients, if necessary.
2. Blend the ingredients from Step 1.
3. Wet granulate the blend from Step 2 with water for injection.
4. Extrude the wet mass from Step 3.

5. Spheronize the extrudate from Step 4.
6. Dry the beads from Step 5.
7. Screen the beads from Step 6 to obtain the appropriately sized fraction.

Enteric Coating of the Core Beads to 30% Polymer Level: (Pravastatin Sodium Modified Release Enteric Coated Beads for Capsules, 7.0% w/w):

a. Composition:

A. BEADS:

Ingredient	Amount Per g
Pravastatin Sodium Beads for Capsules, 10% w/w	0.697 g
(Containing Calcium Carbonate)	
Total Uncoated Beads Weight	0.697 g

B. ENTERIC COAT:

Ingredient	Amount Per g
Eudragit L30D-55, NF (Dry Weight)	0.260 g
Diethyl Phthalate, NF	0.039 g
Total Weight of the Enteric Coat	0.299 g

C. DUSTING:

Ingredient	Amount Per g
Talc, USP	0.005 g
Total Weight of the Enteric Coated Beads	1.000 g

b. Procedure:

ENTERIC COATING SUSPENSION PREPARATION:

1. Weigh the Eudragit L30D-55 suspension.
2. Filter the Eudragit L30D-55 suspension from Step 1.
3. Weigh and slowly add the Diethyl Phthalate to the filtered Eudragit L30D-55 suspension from Step 2 and mix.

4. Weigh and add the required amount of Water for Injection to the Eudragit L30D-55 and Diethyl Phthalate mixture from Step 3 and mix.

BEAD COATING:

- Weigh the Pravastatin Sodium Beads for Capsules, 10% w/w (containing calcium carbonate as the basifying agent)
- Film coat the Pravastatin Sodium Beads for Capsules, 10% w/w (containing calcium carbonate as the basifying agent) with the coating suspension using a fluid bed processor.
- Dry the coated beads.

DUSTING OF THE COATED BEADS:

- Dust the coated beads with talc in a tumbling mixer.

Filling of Enteric-Coated Beads in Capsules

Ingredient	Amount Per Capsule
Pravastatin Sodium Modified Release Enteric Coated Beads for Capsules, 7.0% w/w	287.2 mg
White, Opaque, Size #1 Capsule Shell	One Capsule

FORMULATION 8

Preparation of Core Beads (Pravastatin Sodium Beads for Capsules, 20% w/w) As in Formulation 5.

Enteric Coating of the Core Beads to 20% Polymer Level: (Pravastatin Sodium Modified Release Film Coated Beads for Capsules, 16% w/w):

a. Composition of Enteric Coated Beads

A. Beads:

Ingredient	Amount Per Kg
Pravastatin Sodium Beads for Capsules,20% w/w	0.7960 Kg
Total Uncoated Beads Weight	0.7960 Kg

B. FILM COAT:

Ingredient	Amount Per Kg
Eudragit L30D-55, NF (Dry Weight)	0.1730 Kg
Diethyl Phthalate, NF	0.0260 Kg
Total Weight of the Film Coat	0.1990 Kg

C. DUSTING:

Ingredient	Amount Per Kg
Talc, USP	0.0050 Kg
Total Weight of the Film Coated Beads	1.0000 Kg

b. Procedure for Enteric Coating of Core Beads:

ENTERIC COATING SUSPENSION PREPARATION:

1. Filter the Eudragit L30D-55 suspension.
2. Weigh the Eudragit L30D-55 suspension Step 1.
3. Weigh and slowly add the Diethyl Phthalate to the filtered Eudragit L30D-55 suspension from Step 2 and mix.

BEAD COATING:

- Weigh the "Pravastatin Sodium Beads for Capsules, 20% w/w".
- Film coat the "Pravastatin Sodium Beads for Capsules, 20% w/w",with the coating suspension using a fluid bed processor.
- Dry the coated beads.

DUSTING OF THE COATED BEADS:

- Dust the coated beads with talc in a tumbling mixer.

Enteric Coating of the Core Beads to 40% Polymer Level: (Pravastatin Sodium Modified Release Film Coated Beads for Capsules, 12% w/w):

a. Composition of Enteric Coated Beads

A. Beads:

Ingredient	Amount Per Kg
Pravastatin Sodium Beads for Capsules, 20% w/w	0.5970 Kg
Total Uncoated Beads Weight	0.5970 Kg

B. FILM COAT:

Ingredient	Amount Per Kg
Eudragit L30D-55, NF (Dry Weight)	0.3461 Kg
Diethyl Phthalate, NF	0.0519 Kg
Total Weight of the Film Coat	0.3980 Kg

C. DUSTING:

Ingredient	Amount Per Kg
Talc, USP	0.0050 Kg
Total Weight of the Film Coated Beads	1.0000 Kg

b. Procedure for Enteric Coating of Core Beads:

ENTERIC COATING SUSPENSION PREPARATION:

1. Filter the Eudragit L30D-55 suspension.
2. Weigh the Eudragit L30D-55 suspension Step 1.
3. Weigh and slowly add the Diethyl Phthalate to the filtered Eudragit L30D-55 suspension from Step 2 and mix.

BEAD COATING:

- Weigh the "Pravastatin Sodium Beads for Capsules, 20% w/w".
- Film coat the "Pravastatin Sodium Beads for Capsules, 20% w/w",with the coating suspension using a fluid bed processor.
- Dry the coated beads.

DUSTING OF THE COATED BEADS:

- Dust the coated beads with talc in a tumbling mixer.

FILLING OF ENTERIC COATED BEADS IN CAPSULES
(40 mg Strength)

Ingredient	Amount Per Capsule
Pravastatin Sodium Modified Release Enteric Coated Beads for Capsules, 16% w/w	125.6 mg
Pravastatin Sodium Modified Release Enteric Coated Beads for Capsules, 12% w/w	167.5 mg
White, Opaque, Size #1 Capsule Shell	One Capsule

FORMULATION 9

Preparation of the Core Beads (Pravastatin Sodium Beads for Capsules, 10% w/w):
Same as Formulation 1.

Sub-Coating of the Core Beads to 2% Hydroxypropyl Methylcellulose Polymer Level: (Pravastatin Sodium Subcoated Beads for Capsules, 9.8% w/w):

a. Composition:

A. BEADS:

Ingredient	Amount Per g
Pravastatin Sodium Beads for Capsules, 10% w/w	0.980 g
Total Uncoated Beads Weight	0.980 g

B. SUBCOAT:

Ingredient	Amount Per g
Methocel E3(Hydroxypropyl Methylcellulose), NF (Dry Weight)	0.020 g
Total Weight of the Subcoat	0.020 g

b. Procedure:

COATING SUSPENSION PREPARATION:

1. Weigh the Methocel E3(Hydroxypropyl Methylcellulose).
2. Weigh the required amount of Water for Injection.
3. Slowly add the Methocel E3 (Hydroxypropyl Methylcellulose) from Step 1 to the weighed Water for Injection in Step 2 and stir.

BEAD COATING:

- Weigh the Pravastatin Sodium Beads for Capsules, 10% w/w
- Subcoat the Pravastatin Sodium Beads for Capsules, 10% w/w with the coating suspension using a fluid bed processor.
- Dry the coated beads.

Enteric Coating of the Subcoated Beads to 30% Polymer Level: (Pravastatin Sodium Modified Release Film Coated Beads with a Subcoat for Capsules, 6.8% w/w): __

a. Composition:

A. BEADS:

Ingredient	Amount Per g
Pravastatin Sodium Subcoated Beads for Capsules, 9.8% w/w	0.697 g
Total Uncoated Beads Weight	0.697 g

B. ENTERIC COAT:

Ingredient	Amount Per g
Eudragit L30D-55, NF (Dry Weight)	0.260 g
Diethyl Phthalate, NF	0.039 g
Total Weight of the Enteric Coat	0.299 g

C. DUSTING:

Ingredient	Amount Per g
Talc, USP	0.005 g
Total Weight of the Enteric Coated Beads	1.000 g

b. Procedure:

ENTERIC COATING SUSPENSION PREPARATION:

1. Weigh the Eudragit L30D-55 suspension.
2. Filter the Eudragit L30D-55 suspension from Step 1.
3. Weigh and slowly add the Diethyl Phthalate to the filtered Eudragit L30D-55 suspension from Step 2 and mix.
4. Weigh and add the required amount of Water for Injection to the Eudragit L30D-55 and Diethyl Phthalate mixture from Step 3 and mix.

BEAD COATING:

- Weigh the Pravastatin Sodium Subcoated Beads for Capsules, 9.8% w/w.

- Enteric coat the Pravastatin Sodium Subcoated Beads for Capsules, 9.8% w/w with the coating suspension using a fluid bed processor.
- Dry the coated beads.

DUSTING OF THE ENTERIC COATED BEADS:

- Dust the coated beads with talc in a tumbling mixer.

Filling of Enteric Beads in Capsules

Ingredient	Amount Per Capsule
Pravastatin Sodium Modified Release Enteric Coated Beads with a subcoat for Capsules, 6.8% w/w	294.1 mg
White, Opaque, Size #1 Capsule Shell	One Capsule

FORMULATION 10

a. Composition of Core Beads

Ingredient	Amount Per g
Pravastatin Sodium	0.4000 KgA
Magnesium Oxide, NF	0.0050 Kg
Yellow Ferric Oxide, NF	0.0010 Kg
Microcrystalline Cellulose, NF	ca. 0.5940 KgB
Purified Water, USP	q.s.C
Total Weight	1.0000 Kg

A. This amount is based on the amount of pravastatin sodium at 100% potency. The exact amount will vary depending on the chemical purity ("as is" potency) of the pravastatin sodium.

B. The amount of microcrystalline cellulose will vary depending on the chemical purity of the pravastatin sodium used.

C. Purified Water is used for processing only and is removed during drying. The preferred amount is 0.4270 Kg. The range is 0.4200 Kg to 0.4300 Kg.

b. Procedure for Preparing Core Beads

1. Weigh the pravastatin sodium, magnesium oxide, yellow ferric oxide, and microcrystalline cellulose, and screen the ingredients, if necessary.
2. Blend the ingredients from Step 1.
3. Wet granulate the blend from Step 2 with purified water.
4. Extrude the wet mass from Step 3.
5. Spheronize the extrudate from Step 4.
6. Dry the beads from Step 5.
7. Screen the beads from Step 6 to obtain the appropriately sized fraction.

Enteric Coating of the Core Beads to 30% Polymer Level: (Pravastatin Sodium Modified Release Film Coated Beads for Capsules, 28% w/w):

a. Composition of Enteric Coated Beads

A. BEADS:

Ingredient	Amount Per Kg
Pravastatin Sodium Beads for Capsules, 40% w/w	0.6965 Kg
Total Uncoated Beads Weight	0.6965 Kg

B. FILM COAT:

Ingredient	Amount Per Kg
Eudragit L30D-55, NF (Dry Weight)	0.2596 Kg
Diethyl Phthalate, NF	0.0389 Kg
Total Weight of the Film Coat	0.2985 Kg

C. DUSTING:

Ingredient	Amount Per Kg
Talc, USP	0.0050 Kg
Total Weight of the Film Coated Beads	1.0000 Kg

b. Procedure for Enteric Coating of Core Beads:

ENTERIC COATING SUSPENSION PREPARATION:

1. Filter the Eudragit L30D-55 suspension
2. Weigh the Eudragit L30D-55 suspension from Step 1.
3. Weigh and slowly add the Diethyl Phthalate to the filtered Eudragit L30D-55 suspension from Step 2 and mix.

BEAD COATING:

- Weigh the "Pravastatin Sodium Beads for Capsules, 40% w/w.
- Film coat the "Pravastatin Sodium Beads for Capsules, 40% w/w", with the coating suspension using a fluid bed processor.
- Dry the coated beads.

DUSTING OF THE COATED BEADS:

- Dust the coated beads with talc in a tumbling mixer.

FILLING OF ENTERIC COATED BEADS IN CAPSULES
(80 mg Strength)

Ingredient	Amount Per Kg
Pravastatin Sodium Modified Release Film Coated Beads for Capsules, 28% w/w	287.2 mg
White, Opaque, Size #1 Capsule Shell	One Capsule

FORMULATION 11

a. Composition of Core Beads

Ingredient	Amount Per g
Pravastatin Sodium	0.8000 KgA
Magnesium Oxide, NF	0.0050 Kg
Yellow Ferric Oxide, NF	0.0010 Kg
Microcrystalline Cellulose, NF	ca. 0.1940 KgB
Purified Water, USP	q.s.C
Total Weight	1.0000 Kg

A. This amount is based on the amount of pravastatin sodium at 100% potency. The exact amount will vary depending on the chemical purity ("as is" potency) of the pravastatin sodium.

B. The amount of microcrystalline cellulose will vary depending on the chemical purity of the pravastatin sodium used.

C. Purified Water is used for processing only and is removed during drying. The preferred amount is 0.3000 Kg. The range is 0.2900 Kg to 0.3100 Kg.

b. Procedure for Preparing Core Beads

1. Weigh the pravastatin sodium, magnesium oxide, yellow ferric oxide, and microcrystalline cellulose, and screen the ingredients, if necessary.
2. Blend the ingredients from Step 1.
3. Wet granulate the blend from Step 2 with purified water.
4. Extrude the wet mass from Step 3.
5. Spheronize the extrudate from Step 4.
6. Dry the beads from Step 5.
7. Screen the beads from Step 6 to obtain the appropriately sized fraction.

Enteric Coating of the Core Beads to 40% Polymer Level: (Pravastatin Sodium Modified Release Film Coated Beads for Capsules, 48% w/w):

a. Composition of Enteric Coated Beads

A. BEADS:

Ingredient	Amount Per Kg
Pravastatin Sodium Beads for Capsules, 80% w/w	0.5970 Kg
Total Uncoated Beads Weight	0.5970 Kg

B. FILM COAT:

Ingredient	Amount Per Kg
Eudragit L30D-55, NF (Dry Weight)	0.3461 Kg
Diethyl Phthalate, NF	0.0519 Kg
Total Weight of the Film Coat	0.3980 Kg

C. DUSTING:

Ingredient	Amount Per Kg
Talc, USP	0.0050 Kg
Total Weight of the Film Coated Beads	1.0000 Kg

b. Procedure for Enteric Coating of Core Beads:

ENTERIC COATING SUSPENSION PREPARATION:

1. Filter the Eudragit L30D-55 suspension
2. Weigh the Eudragit L30D-55 suspension from Step 1.
3. Weigh and slowly add the Diethyl Phthalate to the filtered Eudragit L30D-55 suspension from Step 2 and mix.

BEAD COATING:

- Weigh the "Pravastatin Sodium Beads for Capsules, 80% w/w.

- Film coat the "Pravastatin Sodium Beads for Capsules, 80% w/w", with the coating suspension using a fluid bed processor.
- Dry the coated beads.

DUSTING OF THE COATED BEADS:

- Dust the coated beads with talc in a tumbling mixer.

FILLING OF ENTERIC COATED BEADS IN CAPSULES
(160 mg Strength)

Ingredient	Amount Per Capsule
Pravastatin Sodium Modified Release Film Coated Beads for Capsules, 56% w/w	335.0 mg
White, Opaque, Size #1 Capsule Shell	One Capsule

FORMULATION 12

Preparation of Pravastatin Sodium Beads Containing 40% Enteric Coating

Preparation of Core Beads (Pravastatin Sodium Beads for Capsules, 20% w/w)
As in Formulation 5

Enteric Coating of the Core Beads to 40% Polymer Level: (Pravastatin Sodium Modified Release Film Coated Beads for Capsules, 12% w/w)
As in Formulation 8

Filling of Enteric Coated Beads in Capsules

Ingredient	Amount Per Two Capsules
Pravastatin Sodium Modified Release Enteric Coated Beads for Capsules, 12% w/w (40% enteric coating)	335 mg
White, Opaque, Size #1 Capsule Shell	One Capsule

The above formulations of the invention provide a core containing pravastatin and a basifying agent. The enteric coating will be present in an amount sufficient to protect from gastric acidity and yet release the drug at the desired site for absorption. A 35 g/m^2 coating is desired which translates to 10% w/w coating for a 1 mm (average diameter) core bead of 0.78 mg average weight.

Bioavailability of pravastatin in the above formulations is enhanced over prior art pravastatin formulations (which do not contain an enteric coating) while a substantially greater LDL-C and TG reduction is achieved.

In fact, it has been found that the pravastatin dosage in the formulations of the invention may be decreased by as much as 50% without loss of LDL lowering capability as compared to pravastatin formulations which do not include the enteric coating required in the formulations of the invention. Thus, 10 mg, 20 mg, 40 mg, 80 mg and 160 mg pravastatin formulations in accordance with the invention may have an LDL lowering capability equivalent to 20 mg, 40 mg, 80 mg, 160 mg and 320 mg, respectively, pravastatin formulations which do not include the enteric coating employed in the present invention.

What is claimed is:

1. An enteric coated pravastatin formulation having enhanced bioavailability and efficacy comprising a core and an enteric coating for said core, said core comprising (1) pravastatin and (2) optionally one or more basifying agents; said enteric coating comprising a methacrylic acid copolymer in an amount of at least about 17.5 grams of coating polymer per m^2 surface area of the composition; said enteric coating imparting resistance to acid degradation in a low pH environment of 3 or less, but is capable of releasing pravastatin at a pH of 4 or higher, with the proviso that the formulation is substantially free of polyanionic polymers and/or low molecular weight acids.

2. The formulation as defined in Claim 1 wherein the core is in the form of a bead, beadlet, granule, pellet or particle.

3. The formulation as defined in Claim 2 comprising a plurality of beads contained within a capsule.

4. The formulation as defined in Claim 1 wherein the enteric coating comprises from about 20 to about 210 grams of coating polymer per m^2 surface area of the formulation.

5. The formulation as defined in Claim 1 wherein the enteric coating methacrylic acid copolymer is a methylacrylate/methacrylic acid copolymer or a methylmethacrylate/methacrylic acid copolymer.

6. The formulation as defined in Claim 1 wherein the enteric coating includes a hydrophobic plasticizer which is diethyl phthalate, dibutyl phthalate, dibutyl sebacate, tributyl citrate or Myvacet 940.

7. The formulation as defined in Claim 1 wherein the basifying agent is present in an amount within the range of from about 0.1 to about 15% by weight of the formulation and is an alkali metal oxide, hydroxide or carbonate, an alkaline earth metal hydroxide or carbonate, or ammonium hydroxide, $Al(OH)_3$, magaldrate, sodium acetate, sodium citrate, sodium tartrate, sodium fumarate, sodium

malate, sodium succinate, or dihydroxy aluminum sodium carbonate.

8. The formulation as defined in Claim 1 wherein the enteric coating includes an anti-adherent in an amount from about 0.1 to about 5% by weight of the formulation which is fumed silica, magnesium stearate or talc.

9. The formulation as defined in Claim 1 wherein the enteric coating includes the methacrylic acid copolymer in an amount within the range of from about 70 to about 95% by weight, the plasticizer is present in an amount within the range of from about 5 to about 30% by weight, and the anti-adherent is optionally present in an amount within the range of from about 0.1 to about 5% by weight, all of the above % being based on the solids content of the enteric coating.

10. The formulation as defined in Claim 9 wherein the enteric coating includes a methacrylic acid copolymer, diethyl phthalate and talc.

11. The formulation as defined in Claim 1 comprising a plurality of enteric coated beads of different enteric coating levels and/or different amounts of pravastatin and/or different size beads.

12. The composition as defined in Claim 1 in the form of a bead comprising from about 95 to about 40% by weight of a core bead of an average size of 1 mm in diameter and an average weight of approximately 0.78 mg, from about 0 to about 10% by weight of an optional subcoat and from about 5 to 60% by weight of an enteric coating.

13. The composition as defined in Claim 12 wherein said core is comprised of

	% by weight*
pravastatin	1 to 90
basifying agent	0.1 to 15
filler	10 to 99

(*% based on core weight)

said enteric coating is comprised of

	Range (g/m^2)
methacrylic acid copolymer	17.5 to 161.5**
plasticizer	2.3 to 48.5

(**% based on gram of enteric coating weight per m^2 of core beads).

14. The composition as defined in Claim 13 wherein said basifying agent is MgO or $CaCO_3$, said filler is microcrystalline cellulose, and said plasticizer is diethyl phthalate.

15. The formulation as defined in Claim 1 wherein the beads comprise from about 10 to about 80% pravastatin and have an enteric coating level within the range from about 15 to about 40% w/w which for an average diameter core bead of 1.0 mm and an average weight of 0.78 mg represents from about 52.5 to about 140 grams of enteric coating per m^2 surface area of the core beads.

16. The formulation as defined in Claim 1 comprising 40 mg pravastatin coated at 40% enteric coating level.

17. A prolonged release enteric coated pravastatin bead formulation having enhanced bioavailability and efficacy comprising a plurality of beads each comprising a core containing pravastatin and an enteric coating for said core, said beads comprising a mixture of beads containing different levels or amounts of enteric coating so as to protect pravastatin from acid degradation in the stomach and enable release of substantial amounts of pravastatin into the small intestine, from which it is absorbed into the bloodstream to provide increased pravastatin blood levels and enhanced reduction of LDL- cholesterol and

triglycerides as compared to immediate release pravastatin formulations.

18. The formulation as defined in Claim 17 wherein said bead comprises (1) pravastatin and (2) optionally one or more basifying agents, and (3) an enteric coating and (4) optionally an anti-adherent outer coating.

19. The formulation as defined in Claim 17 wherein the methacrylic acid copolymer is present in an amount to impart resistance to acid degradation in a low pH environment of 3 or less, but is capable of releasing pravastatin at a pH of 4 or higher.

20. The formulation as defined in Claim 17 comprising a plurality of beads contained within one or more capsules wherein beads in the same or different capsules have the same or different enteric coating levels and/or the same or different amount of pravastatin and/or the same or different size beads.

21. The formulation as defined in Claim 17 wherein the enteric coating comprises from about 20 to about 210 grams of coating polymer per m^2 surface area of the formulation.

22. The formulation as defined in Claim 17 wherein the enteric coating methacrylic acid copolymer is a methylacrylate/methacrylic acid copolymer or a methylmethyacrylate/methacrylic acid copolymer.

23. The formulation as defined in Claim 17 wherein the enteric coating includes a hydrophobic plasticizer which is diethyl phthalate, dibutyl phthalate, dibutyl sebacate, tributyl citrate or Myvacet 940.

24. The formulation as defined in Claim 20 wherein the plurality of beads of the same or different size include from about two to about seven portions of beads having a different prescribed enteric coating levels which may be the same or different, each portion having the same or different amounts of pravastatin.

25. The formulation as defined in Claim 17 wherein the plurality of enteric coated beads (which include a

mixture of beads containing different amounts of enteric coating to enable the beads to release of pravastatin substantially throughout the small intestine) include in a 10 to 160 mg dose from about 0 to about 50% by weight of total beads containing from about 17.5 to about 87.5 mg of enteric coating per m^2 surface area of bead, from about 0 to about 60% by weight of total beads containing from about 105 to about 140 mg of enteric coating per m^2 surface area of bead, and/or from about 0 to about 60% by weight of total beads containing from about 140 to about 210 mg of enteric coating per m^2 surface area of bead, which translates to from about 5% to about 60% by weight enteric coating based on the weight of the final pravastatin bead dosage form (average diameter of about 1 mm and weight of about 0.78 mg per bead).

26. The formulation as defined in Claim 17 wherein the plurality of beads is contain in a single capsule or in a plurality of capsules, (1) at least one capsule of which includes pravastatin beads containing the same or a different amounts of pravastatin having an enteric coating level which differs from capsule to capsule, or (2) at least one capsule of which includes the same mixture of beads containing the same or different amounts of pravastatin and/or the same or different enteric coating levels or (3) at least one capsule includes a mixture of beads of varying size which beads include the same or different amounts of pravastatin and the same or different enteric coating levels.

27. The formulation as defined in Claim 20 comprising

(1) 20 mg pravastatin coated at 15% coating level, 12 mg pravastatin coated at 25% coating level, and 8 mg pravastatin coated at 40% coating level; or

(2) 10 mg Pravachol® tablets, 10 mg pravastatin coated at 15% coating level; 10 mg pravastatin coated at 25% coating level; and 10 mg pravastatin coated at 40% coating level; or

(3) 10 mg pravastatin coated at 15% coating level; 12 mg pravastatin coated at 25% coating level, and 18 mg pravastatin coated at 40% coating level; or

(4) 20 mg pravastatin coated at 20% coating level, and 20 mg pravastatin coated at 40% coating level.

28. The formulation as defined in Claim 17 which is designed to release substantial amounts of pravastatin into the duodenum, jejunum and ileum.

29. The formulation as defined in Claim 17 wherein the core bead comprises

pravastatin sodium
magnesium oxide
microcrystalline cellulose

and the enteric coating comprises

methacrylic acid copolymer
diethyl phthalate
and talc

with the amount of pravastatin present varying from about 10 to about 25% w/w and the amount of enteric coating varying from about 15 to about 40% w/w.

30. An enteric coated pharmaceutical composition comprising a core in the form of a beadlet, pellet, granule or particle and an enteric coating for said core, said core comprising an acid labile medicament which is pravastatin in an amount within the range from about 50 to about 100% by weight of said composition, a binder in an amount within the range from about 0 to about 10% by weight of said composition, a disintegrant in an amount within the range of from about 0 to about 10% by weight of said composition, and said enteric coating comprising a methacrylic acid copolymer and a plasticizer, said enteric coating imparting protection to said core so that said core is afforded protection in a low pH environment of 3 or less while capable of releasing medicament at a pH of 4.5 or higher, said pharmaceutical composition also comprising an anti-adherent in an amount within the range of from about 0.1 to about 4.0% by weight.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/28375

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 9/58, 9/50
US CL :424/462, 497
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/462, 497

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

NONE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5,225,202 A (HODGES et al) 06 July 1993(06.07.93), see entire document.	1-30
Y	US 5,158,777 A (ABRAMOWITZ et al) 27 October 1992(27.10.92), see entire document.	1-30

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
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